I-11 Towards an HIV vaccine – what is protective immunity against HIV infection?

S. Rowland-Jones*. *Nuffield Department of Medicine, Oxford University, John Radcliffe Hospital, Oxford, UK*

Following the disappointment experienced after the failure of the STEP HIV phase II vaccine trial last year, questions have been raised about whether or not an effective vaccine to prevent HIV-1 infection can ever be achieved. Some have argued that the trial should be seen as a product failure rather than a failure of the entire T-cell vaccine concept, and that clinical vaccine studies should continue on an empirical basis. Others have suggested that there should be a return to basic science in order to define genuine correlates of protective immunity against HIV-1 infection. This presentation will review the current obstacles facing HIV vaccine development and discuss our understanding of the requirements for a successful HIV-1 vaccine. Studies of HIV-2 infection in West Africa will be presented to provide support for the concept of protective immunity.

I-12 Vaccination against varicella and zoster: history and experience in the United States

A.A. Gershon*. *Department of Pediatrics, Columbia University Medical Center, New York, USA*

Live attenuated varicella vaccine (Oka strain) was developed in Japan by Professor M. Takahashi and his colleagues in the early 1970s. This vaccine is the only live herpesvirus vaccine in use today. While initially designed to prevent varicella (chickenpox), it is also now employed to prevent zoster as well, in a somewhat stronger formulation than that used to prevent varicella. At present the vaccine is about 85% effective in preventing childhood varicella and 50% effective in preventing zoster in elderly adults with a past history of natural varicella. To prevent varicella, the rationale is that immunity to varicella-zoster virus (VZV) similar to that following natural infection occurs and prevents subsequent infection with wild type VZV. To prevent zoster, the rationale is to boost cellular immunity (CMI) to VZV in individuals who have lost this form of immunity decades after chickenpox; in this instance the vaccine is therapeutic.

This presentation will review the safety, immunogenicity, and protection data for varicella vaccine and the zoster vaccine. Both of these vaccines have proven to be extremely safe and effective. Varicella vaccine is being used on a world wide basis and is used university for children in a number of countries, including the United States and Canada. In the United States alone, over 50 million doses of the vaccine have been distributed for suspceptible children and adults. In the United States, the incidence of varicella and its associated morbidity and mortality in otherwise healthy children has fallen by roughly 80%, not only in the vaccinated but in the unvaccinated as well, indicating herd immunity. Zoster results when latent VSV (after chickenpox or vaccination) reactivates; the incidence of zoster in vaccines appears to be lower than after the natural infection. Vaccinated individuals extremely rarely transmit the Oka strain to others. The duration of immunity to VZV after vaccination is currently under study, but thus far appears to be long lasting in most vaccinees.

I-13 Pathogenesis and treatment of bird flu

K.Y. Yuen*. *Department of Microbiology, University of Hong Kong, China*

Influenza A/H5N1 virus kills more than 50% of those infected. Clinical observation suggested that this disease is not simply a viral pneumonia, and that all other major organs could be affected due to a cytokine storm caused by virus-induced aberrant immune activation. Unlike seasonal influenza caused by the human virus, which usually can only be isolated in the respiratory secretions, the A/H5N1 virus can also be found in the blood, faeces, and cerebrospinal fluid. Thus, this so-called cytokine storm could be the end result of uncontrolled systemic viral infection as in severe septic shock due to poorly treated Gram negative bacteraemia. The option of antiviral therapy is very limited, because resistance to adamantanes is widespread in A/H5N1 isolates from Vietnam and Thailand. Zanamivir is only likely to be useful for prophylaxis in health care workers, because it is delivered by inhalation and not expected to reach therapeutic concentrations in extrapulmonary tissues or hypoventilated areas of lung consolidation. Intravenous zanamivir, peramivir and viramidine are not yet available and intravenous ribavirin has many side effects. Treatment with oseltamivir did not obviously result in improved survival and emergence of resistance during treatment is not uncommon, but there was a trend towards better survival if given early in the course of illness. Since the lymphopaenia and serum pro-inflammatory cytokine levels correlate directly with the viral load in respiratory secretions, it is also reasonable to consider giving immunomodulators to dampen the cytokine storm. However, the use of steroids did not improve survival and was associated with significant complications such as hyperglycaemia and superinfection. In fact, after knockout of pro-inflammatory chemokine and cytokine genes or treatment with steroids, A/H5N1 virus-infected mouse models showed no significant improved survival. Data from mice models suggest that high dose of oseltamivir therapy prolonged to more than 8 days, combination of oseltamivir with amantadine, and use of high titres of neutralising monoclonal antibody or convalescent plasma, may improve survival. Cyclooxygenase-2 (COX-2) was strongly induced in H5N1-infected macrophages in vitro and in epithelial cells of lung tissue samples obtained during autopsy of infected patients. COX-2, along with tumor necrosis factor alpha and other proinflammatory cytokines were hyperinduced in epithelial cells by secretory factors from H5N1-infected macrophages in vitro. Zanamivir combined with non-steroidal immunomodulators may have some effect on improving survival.